·综述·

牙龈卟啉单胞菌在消化系统肿瘤发生发展中的角色和相关机制

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【摘要】牙周炎关键病原体牙龈卟啉单胞菌（*P. gingivalis*）的致病作用已远超口腔局部范畴，*P. gingivalis* 可在消化系统肿瘤组织中被特异性检出，且其感染丰度与肿瘤的侵袭转移能力、患者不良预后密切相关。本研究系统梳理 *P. gingivalis* 与口腔癌、食管癌、胰腺癌、肝癌及结直肠癌等消化系统肿瘤关联的基础与临床研究，深入剖析该菌诱导肿瘤发生发展的潜在分子机制，旨在为消化系统肿瘤的风险预警、早期诊断及靶向治疗提供新的理论依据与研究方向。

【关键词】牙龈卟啉单胞菌；消化系统；肿瘤发生发展；分子机制
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Role and related mechanisms of *Porphyromonas gingivalis* in the occurrence and development of digestive system tumors

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【Abstract】The pathogenic role of *Porphyromonas gingivalis* (*P. gingivalis*), a key pathogen in periodontitis, has been well documented to extend far beyond the oral cavity. *P. gingivalis* can be specifically detected in digestive system tumor tissues, and its infection abundance is closely associated with tumor invasion, metastasis, and poor prognosis in patients. This study systematically reviews basic and clinical research on the association between *P. gingivalis* and digestive system tumors including oral cancer, esophageal cancer, pancreatic cancer, liver cancer, and colorectal cancer. The potential molecular mechanisms underlying *P. gingivalis*-induced tumor initiation and progression were further elucidated thoroughly, aiming to provide new theoretical basis and research directions for risk warning, early diagnosis, and targeted therapy of digestive system tumors.

【Keywords】*Porphyromonas gingivalis*; Digestive system; Tumor pathogenesis and progression; Molecular mechanism

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牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*P. gingivalis*）可特异性黏附于牙龈上皮细胞及牙龈成纤维细胞，与牙周病的发生发展存在密切关联[1]。流行病学研究表明，*P. gingivalis* 在健康人群中感染率约 20%，而肿瘤患者感染率可超过 40%[2-3]。*P. gingivalis* 可通过脂多糖（lipopolysaccharide，LPS）、牙龈蛋白酶、菌毛蛋白（fimbrillin，FimA）等多种毒力因子参与消化系统疾病的发生发展。例如，LPS 可调控口腔癌相关基因的表达[4]；牙龈蛋白酶能通过多种机制影响结直肠癌的进展[5]；而 FimA 可通过调控上皮间质转化（epithelial-mesenchymal transition，EMT）[6]、免疫及代谢相关基因表达[7]等机制促进癌症进展。多项研究在消化系统肿瘤患者的口腔、血清及肿瘤样本中检出 *P. gingivalis*[4, 8-9]，且检出差异与肿瘤进展及不良预后密切相关[10-11]。

上述证据提示，*P. gingivalis* 可能参与并介导消化系统肿瘤的发生与发展过程。基于此，本文综述 *P. gingivalis* 与口腔癌、食管癌、胰腺癌、肝癌及结直肠癌相关的临床和基础研究证据，旨在揭示其在消化系统肿瘤发生发展中的作用及潜在分子机制。

1 *P. gingivalis*与消化系统肿瘤的流行病学研究

流行病学研究显示，*P. gingivalis* 与消化系统肿瘤的发生发展密切相关。口腔鳞状细胞癌（oral squamous cell carcinoma，OSCC）患者的 *P. gingivalis* 唾液检出率、血清抗体水平均显著高于健康人群[4, 12-13]，且癌组织内 *P. gingivalis* 丰度与患者生存期缩短相关[14-16]。食管鳞状细胞癌（esophageal squamous cell carcinoma，ESCC）患者牙龈菌斑中 *P. gingivalis* 丰度及血清抗体水平显著升高[3, 17]，癌组织内该菌定植状态与肿瘤分化程度、淋巴结转移、临床分期及疾病预后密切相关[18-20]。在胰腺癌中，患者口腔 *P. gingivalis* 检出率显著高于健康人群，血清抗体水平升高与胰腺癌发病风险增加相关[8, 21-22]；同时，唾液中该菌丰度越高，患者生存期越短，且胰腺癌组织中也可检测到 *P. gingivalis* 定植[23-24]。研究表明，*P. gingivalis* 感染与非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH）的发生和进展相关，而 NASH 可发展为 NASH 相关肝癌（NASH-associated liver cancer，NALC）[25-26]。此外，在代谢功能障碍相关性脂肪性肝炎相关肝细胞癌（hepatocellular carcinoma，HCC）患者唾液中，*P. gingivalis* 丰度显著高于脂肪性肝炎患者，提示该菌可能参与 HCC 的发生过程[27]。结直肠癌（colorectal cancer，CRC）患者粪便中 *P. gingivalis* 检出率显著升高，且与黏液腺癌分型、不良预后密切相关[28-29]；同时，肠黏膜及癌组织中 *P. gingivalis* 定植状态与 CRC 微卫星不稳定性免疫分型存在显著关联[30]。综上所述，*P. gingivalis* 可能通过多种潜在机制参与消化系统肿瘤的发生、进展及预后调控。

2 *P. gingivalis*与消化系统肿瘤发生发展相关机制的研究证据

2.1 *P. gingivalis*与口腔癌

P. gingivalis 可通过调控细胞 EMT、增殖、侵袭及自噬多种生物学过程，参与 OSCC 发生与进展。*P. gingivalis* 通过上调 OSCC 细胞中白介素-8（interleukin-8，IL-8）、基质金属蛋白酶-1（matrix metalloproteinase-1，MMP-1）及 MMP-10 的表达诱导 EMT[31]，同时活化整合素 αV 及黏着斑激酶（focal adhesion kinase，FAK）信号，协同增强 OSCC 细胞的迁移与侵袭能力[32]。此外，该菌可通过诱导癌症干细胞标志物 CD44、CD133 的表达[31]，并通过激活含核苷酸结合寡聚化结构域 1（NOD1）/Krüppel 样因子 5 通路，上调脂质代谢关键酶硬脂酰辅酶 A 去饱和酶 1 的表达，进而增强 OSCC 细胞的干性特征[33]。*P. gingivalis* 标准株 33277 与 W83 可通过 miR-21/ 程序性细胞死亡因子 4/ 激活蛋白 1 负反馈环路调控细胞周期蛋白 D1 的表达，其中 33277 菌株还可通过诱导自噬、抑制细胞凋亡，进一步调控 OSCC 细胞的增殖与存活[34-35]。

除核心调控机制外，*P. gingivalis* 的不同菌株及多种菌体成分也可通过特异性途径影响 OSCC 的发生发展。其中，33277 菌株可通过上调口腔上皮细胞中磷酸化糖原合酶激酶-3β 的水平，以及 Slug、Snail 等 EMT 相关分子及 MMP-2 表达，诱导口腔上皮细胞 EMT 及恶性转化[36]。33277 菌株还可通过募集肿瘤相关中性粒细胞，激活 C-X-C 趋化因子配体（CXCL）2/C-X-C 趋化因子受体 2 轴及 JAK1/STAT3 信号通路，增强肿瘤

侵袭与增殖能力并促进 OSCC 生长[15]。此外，381 菌株可通过 Toll 样受体（toll-like receptor，TLR）与口腔上皮细胞相互作用，诱导小鼠口腔肿瘤发生，并通过 IL-6/STAT3 轴促进肿瘤进展[37]；不同菌株的 FimA 可通过调控锌指 E 盒结合同源框 1（ZEB1）表达及核定位启动 EMT，诱导 OSCC 细胞中 CCL20、CXCL8 等促炎因子上调，进而促进 OSCC 进展[7]。在菌体组分方面，外膜囊泡可通过激活核因子 κB（nuclear factor kappa-B，NF-κB）通路抑制铁死亡[38]，而牙龈蛋白酶可通过激活蛋白酶激活受体 -2（PAR2）和 PAR4、ERK1/2 等信号通路增强 OSCC 细胞侵袭能力[39-40]，LPS 能够促进口腔上皮癌前病变[4]，上述效应共同参与 OSCC 的恶性进展。

P. gingivalis 还可通过多种途径介导 OSCC 细胞免疫逃逸和化疗耐药，从而促进肿瘤进展。免疫逃逸方面，*P. gingivalis* 可诱导中性粒细胞胞外诱捕网释放，包裹 OSCC 细胞，增强其迁移和侵袭能力，同时诱导 OSCC 细胞程序性死亡受体配体 1（programmed death-ligand 1，PD-L1）和 B7-DC 受体表达，抑制 T 细胞活化[41-42]。*P. gingivalis* 菌膜可上调 TLR、NF-κB 及丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）通路基因，调控免疫逃逸[43]。膜蛋白抑制骨髓来源巨噬细胞对 OSCC 细胞的吞噬，诱导其向 M2 型极化[44]。化疗耐药方面，*P. gingivalis* 通过活化 Notch1 信号及上调 IL-6 表达，增强 OSCC 细胞对紫杉醇的耐药性，增加移植瘤成瘤及肺转移风险[45-46]。

综上所述，*P. gingivalis* 通过多种机制参与 OSCC 发生发展，清除口腔内 *P. gingivalis* 及靶向其促癌分子可能成为 OSCC 的有效防治策略。

2.2 *P. gingivalis*与食管癌

P. gingivalis 可通过调控细胞恶性转化、肿瘤微环境、免疫逃逸及化疗耐药等多种机制，参与 ESCC 的发生与发展。该菌可通过下调紧密连接相关基因的表达，诱导正常食管上皮细胞恶性转化[47]，并通过激活 miR-194/GRHL3/PTEN/AKT 信号通路，显著增强 ESCC 细胞增殖与迁移能力[48]。此外，*P. gingivalis* 可下调 ESCC 细胞干扰素 -γ 受体 1（interferon γ receptor subunits 1，IFNGR1）表达并促进 IFNGR1 蛋白 122 位点棕榈酰化，及激活 NF-κB 信号通路，促进 ESCC 细胞增殖、侵袭及迁移[49-50]。*P. gingivalis* 可通过调控 EMT 及募集骨髓来源抑制细胞，诱发促炎肿瘤微环境，加速肿瘤细胞生长和进展[51-52]；其 FimA 还可通过上调 ESCC 细胞糖蛋白 A 为主的重复序列表达，激活转化生长因子 β/Smad 信号通路，促进肿瘤生长和肺转移[53]。

在 ESCC 免疫逃逸与化疗耐药调控中，*P. gingivalis* 同样发挥重要作用。该菌通过上调赖氨酸去甲基化酶 5B 表达抑制 T 细胞聚集，同时上调免疫检查点分子 B7-H4 表达抑制活化 $CD8^+$ T 细胞增殖，两种分子共表达加剧抑制效应，协同促进 ESCC 免疫逃逸[54]；同时，*P. gingivalis* 可通过上调 YTH N6- 甲基腺苷 RNA 结合蛋白 2 表达，降低 ESCC 细胞中 Fas 蛋白表达水平，协助肿瘤细胞逃避免疫系统的监视[55]。生物信息学分析显示，*P. gingivalis* 感染与肿瘤微环境促炎表型相关，可导致树突细胞活化水平、2 型 T 辅助细胞及中性粒细胞等免疫细胞浸润水平降低[56]。在化疗耐药方面，FimA 可通过抑制程序性细胞死亡因子 4 表达诱导 ESCC 细胞中癌症干细胞富集，或上调磷酸化糖原合酶激酶 -3β 蛋白表达并通过其介导的线粒体氧化磷酸化途径，增强细胞对紫杉醇等化疗药物的耐药性，加剧恶性表型[57-58]。

综上，*P. gingivalis* 可通过上述多种机制参与 ESCC 病理进程，而靶向 *P. gingivalis* 及其介导的关键分子机制进行干预有望为 ESCC 防治提供新策略。

2.3 *P. gingivalis*与胰腺癌

P. gingivalis 可通过诱导胰腺导管上皮细胞恶性转化、重塑肿瘤免疫微环境等多种途径参与胰腺癌的发生发展进程。*P. gingivalis* 可从口腔迁移定植于胰腺，改变局部微生态结构，诱导腺泡细胞增殖，直接驱动胰腺癌前病变胰腺上皮内瘤变（pancreatic intraepithelial neoplasia，PanIN）的发生与进展[59]。动物实验表明，*P. gingivalis* 可下调转基因小鼠 EMT 标志物 Snail-1、ZEB1，以及胶原纤维、Gal-3、PD-L1 的表达，进一步推动 PanIN 进展[60]。*P. gingivalis*-LPS 可诱导小鼠胰腺胰岛再生源蛋白表达上调，进一步参与胰腺癌发生过程[61]。缺氧微环境能够显著促进 *P. gingivalis* 在胰腺癌细胞内增殖，以不依赖 TLR2 的方式增强癌细胞增殖与成瘤能力，并保护癌细胞免受活性氧介导的细胞死亡[59, 62]。同时，*P. gingivalis* 可

重塑肿瘤微环境，形成以中性粒细胞为主导的促炎状态，提升癌细胞体内成瘤能力，而中性粒细胞释放的趋化因子与弹性蛋白酶可进一步促进胰腺癌进展[23]。

综上，现有研究证实 *P. gingivalis* 参与胰腺癌发生和发展，针对该菌靶向干预有望成为调控胰腺癌发病风险、延缓疾病进展的潜在策略。

2.4 *P. gingivalis*与非酒精性脂肪性肝炎相关肝癌

P. gingivalis 可通过调节整合素信号通路与 TNF-α 介导的 DNA 氧化损伤，加速高脂饮食诱导的 NASH 小鼠模型肿瘤结节形成[63]。而且，在体外肝癌细胞模型中，*P. gingivalis* 可诱导小鼠肝癌细胞株 Hepa-1.6 分泌 TNF-α、IL-6 等促炎因子，通过诱发持续性炎症反应推动肿瘤进展[64]。

综上，*P. gingivalis* 通过促使 NASH 进展间接参与 NALC 发生发展，但其在直接诱导 HCC 发生发展分子机制上有待更多深入研究予以证实。

2.5 *P. gingivalis*与结直肠癌

研究表明 *P. gingivalis* 可通过塑造促炎微环境、调控免疫逃逸及影响肿瘤血管生成等多重机制，参与 CRC 的发生与发展进程。在 *APC* 基因突变小鼠中，*P. gingivalis* 能选择性富集肿瘤浸润髓系细胞，诱导 TNF-α、IL-6、IL-1β 等促炎因子水平升高，构建促炎微环境，驱动肿瘤发生与发展；同时，激活血源性 NOD 样受体家族蛋白 3 炎性小体，进一步强化促癌免疫微环境，促进结肠肿瘤进展[29]。此外，*P. gingivalis* 可通过上调壳多糖酶 3 样蛋白 1 的表达，阻碍恒定自然杀伤 T 细胞裂解，损害其细胞毒性功能并诱导其向促肿瘤表型转化，促进宿主肿瘤细胞免疫逃避，加速 CRC 进展[65]。*P. gingivalis* 33277 菌株可通过激活 MAPK/ERK 信号通路促进 CRC 细胞增殖，而牙龈蛋白酶突变缺陷株 KDP136 的促增殖能力显著减弱，提示牙龈蛋白酶活性是 *P. gingivalis* 介导 CRC 细胞增殖的关键毒力因子[28]。

在免疫逃逸与血管生成调控中，菌体成分发挥关键作用。*P. gingivalis* W83 菌株的全膜成分和肽聚糖，可通过激活 NOD1/NOD2、受体相互作用蛋白 2、MAPK 信号通路，上调 CRC 细胞 PD-L1 表达，介导免疫逃逸[30]。此外，*P. gingivalis* 的热休克蛋白 GroEL 可通过上调内皮型一氧化氮合酶表达、活化 p38 MAPK 信号促进内皮祖细胞迁移及小管形成，促进结肠癌移植瘤生长并加速荷瘤小鼠死亡，表明 GroEL 可能通过促进肿瘤新生血管生成，加速 CRC 恶性进展[66]。

综上，*P. gingivalis* 可通过直接定植及促炎机制参与 CRC 发生与进展，清除该菌及靶向其致病机制有望为 CRC 的防治提供新策略。

3 结语

P. gingivalis 可通过调控肿瘤微环境、炎症反应、细胞迁移与侵袭、免疫逃逸及治疗耐药等多种途径，在消化系统肿瘤进展中发挥关键驱动作用，其 LPS、牙龈蛋白酶、FimA 等关键毒力因子介导的局部及全身免疫调控，是决定该菌影响不同消化系统肿瘤发生发展模式与分子机制的核心要素。因此，深入解析 *P. gingivalis* 调控肿瘤细胞恶性表型的具体机制，挖掘其介导消化系统肿瘤进展的关键治疗靶点与诊断标志物，并建立针对不同毒力成分的靶向干预与清除策略，有望为消化系统肿瘤的临床防治提供全新思路与有效策略。

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